

=> fil cap  
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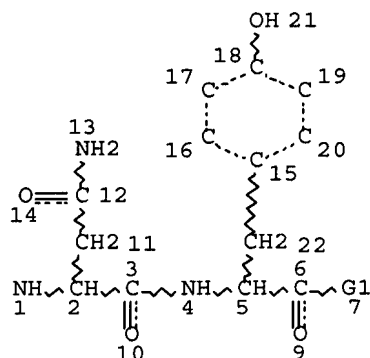
FILE COVERS 1907 - 26 Sep 2007 VOL 147 ISS 14  
 FILE LAST UPDATED: 25 Sep 2007 (20070925/ED)

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=> d que 139

L23 STR



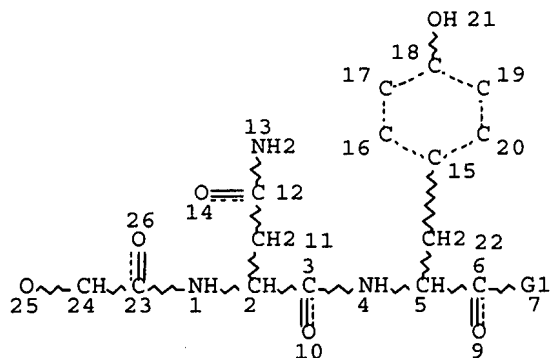
VAR G1=NH2/OH  
 NODE ATTRIBUTES:  
 CONNECT IS E2 RC AT 16  
 CONNECT IS E2 RC AT 17  
 CONNECT IS E2 RC AT 19  
 CONNECT IS E2 RC AT 20  
 DEFAULT MLEVEL IS ATOM  
 DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:  
 RING(S) ARE ISOLATED OR EMBEDDED  
 NUMBER OF NODES IS 21

STEREO ATTRIBUTES: NONE  
 L25 1260 SEA FILE=REGISTRY SSS FUL L23

L26

STR



VAR G1=NH2/OH

NODE ATTRIBUTES:

CONNECT IS E2 RC AT 16

CONNECT IS E2 RC AT 17

CONNECT IS E2 RC AT 19

CONNECT IS E2 RC AT 20

DEFAULT MLEVEL IS ATOM

DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:

RING(S) ARE ISOLATED OR EMBEDDED

NUMBER OF NODES IS 25

STEREO ATTRIBUTES: NONE

L28 2 SEA FILE=REGISTRY SUB=L25 SSS FUL L26

L29 1 SEA FILE=REGISTRY ABB=ON PLU=ON L28 AND C17H22N4O7/MF

L39 1 SEA FILE=CAPLUS ABB=ON PLU=ON L29

=&gt; d l39 ibib abs hitstr

L39 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2007:61250 CAPLUS Full-text

DOCUMENT NUMBER: 146:143006

TITLE: Preparation of N- or C-terminally modified small peptides for pharmaceutical use

INVENTOR(S): Larsen, Bjarne Due; Kerns, Edward H.

PATENT ASSIGNEE(S): Zealand Pharma A/S, Den.; Kiddle, Simon John

SOURCE: PCT Int. Appl., 54pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

| PATENT NO.    | KIND | DATE     | APPLICATION NO. | DATE     |
|---------------|------|----------|-----------------|----------|
| WO 2007007060 | A2   | 20070118 | WO 2006-GB2527  | 20060707 |
| WO 2007007060 | A3   | 20070405 |                 |          |

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP,

KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN,  
 MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU,  
 SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG,  
 US, UZ, VC, VN, ZA, ZM, ZW  
 RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE,  
 IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ,  
 CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH,  
 GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY,  
 KG, KZ, MD, RU, TJ, TM, AP, EA, EP, OA

US 2007123469 A1 20070531 US 2006-482365 20060707  
 PRIORITY APPLN. INFO.: GB 2005-14071 A 20050707  
 US 2005-697138P P 20050707

OTHER SOURCE(S): MARPAT 146:143006

AB The invention discloses N- or C-terminally modified small peptides having antiarrhythmic and improved pharmacokinetic properties and a reduced tendency to inhibit the activity of isoenzyme 3A4 of cytochrome P 450 oxidase. Thus, N-(hydroxyacetyl)-Gly-Tyr-NH<sub>2</sub> was prepared by the solid-phase method and shown to exhibit antiarrhythmic activity (48.7% response in the calcium-induced arrhythmia assay).

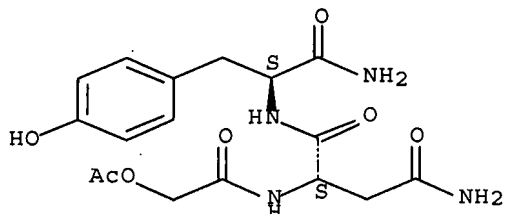
IT 919104-68-0P

RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)  
 (preparation of N- or C-terminally modified small peptides having antiarrhythmic activity)

RN 919104-68-0 CAPLUS

CN L-Tyrosinamide, N2-[2-(acetyloxy)acetyl]-L-asparaginyl- (CA INDEX NAME)

Absolute stereochemistry.



=> fil marpat

FILE 'MARPAT' ENTERED AT 13:21:42 ON 26 SEP 2007

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FILE CONTENT: 1961-PRESENT VOL 147 ISS 14 (20070923/ED)

SOME MARPAT RECORDS ARE DERIVED FROM INPI DATA FOR 1961-1987

MOST RECENT CITATIONS FOR PATENTS FROM MAJOR ISSUING AGENCIES  
 (COVERAGE TO THESE DATES IS NOT COMPLETE):

US 2007191642 16 AUG 2007

DE 102006005768 09 AUG 2007

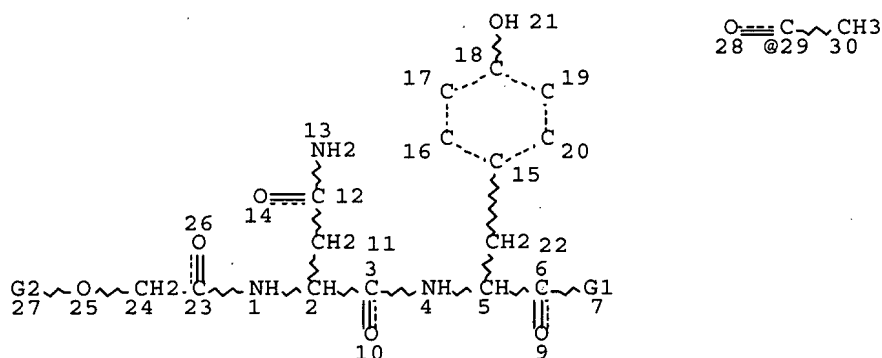
EP 1816181 08 AUG 2007

JP 2007204412 16 AUG 2007  
 WO 2007092531 16 AUG 2007  
 GB 2433499 27 JUN 2007  
 FR 2896886 03 AUG 2007  
 RU 2304584 20 AUG 2007  
 CA 2571093 16 JUN 2007

Expanded G-group definition display now available.

=> d que 144

L41 STR



VAR G1=OH/NH2

VAR G2=H/29

NODE ATTRIBUTES:

CONNECT IS E2 RC AT 16

CONNECT IS E2 RC AT 17

CONNECT IS E2 RC AT 19

CONNECT IS E2 RC AT 20

DEFAULT MLEVEL IS ATOM

DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:

RING(S) ARE ISOLATED OR EMBEDDED

NUMBER OF NODES IS 29

STEREO ATTRIBUTES: NONE

L43 1 SEA FILE=MARPAT SSS FUL L41

L44 1 SEA FILE=MARPAT ABB=ON PLU=ON L43/COM

=> d 144 ibib abs qhit tot

L44 ANSWER 1 OF 1 MARPAT COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 146:143006 MARPAT Full-text

TITLE: Preparation of N- or C-terminally modified small peptides for pharmaceutical use

INVENTOR(S): Larsen, Bjarne Due; Kerns, Edward H.

PATENT ASSIGNEE(S): Zealand Pharma A/S, Den.; Kiddle, Simon John

SOURCE: PCT Int. Appl., 54pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

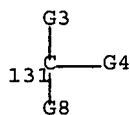
## PATENT INFORMATION:

| PATENT NO.                                                                                                                                                                                                                                                                                                                                                                                                                     | KIND | DATE     | APPLICATION NO. | DATE     |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------|----------|-----------------|----------|
| WO 2007007060                                                                                                                                                                                                                                                                                                                                                                                                                  | A2   | 20070118 | WO 2006-GB2527  | 20060707 |
| WO 2007007060                                                                                                                                                                                                                                                                                                                                                                                                                  | A3   | 20070405 |                 |          |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW  |      |          |                 |          |
| RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AP, EA, EP, OA                                                                                                                     |      |          |                 |          |
| US 2007123469                                                                                                                                                                                                                                                                                                                                                                                                                  | A1   | 20070531 | US 2006-482365  | 20060707 |
| PRIORITY APPLN. INFO.:                                                                                                                                                                                                                                                                                                                                                                                                         |      |          | GB 2005-14071   | 20050707 |
|                                                                                                                                                                                                                                                                                                                                                                                                                                |      |          | US 2005-697138P | 20050707 |
| AB The invention discloses N- or C-terminally modified small peptides having antiarrhythmic and improved pharmacokinetic properties and a reduced tendency to inhibit the activity of isoenzyme 3A4 of cytochrome P 450 oxidase. Thus, N-(hydroxyacetyl)-Gly-Tyr-NH <sub>2</sub> was prepared by the solid-phase method and shown to exhibit antiarrhythmic activity (48.7% response in the calcium-induced arrhythmia assay). |      |          |                 |          |

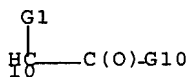
MSTR 1

G<sub>13</sub>-G<sub>12</sub>-G<sub>5</sub>-G<sub>9</sub>

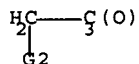
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 G2 = CH<sub>2</sub>CONH<sub>2</sub>  
 G3 = OH  
 G5 = NH  
 G7 = 131



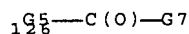
G9 = 10



G10 = OH  
G12 = 3-4 2-6



G13 = 126



Patent location: claim 1  
Note: substitution is restricted  
Note: or pharmaceutically acceptable salts  
Note: or N-oxides, S-oxides, or S-dioxides

=> d que 156

L46 335 SEA FILE=CAPLUS ABB=ON PLU=ON ("LARSEN B"/AU OR "LARSEN B A"/AU OR "LARSEN B B"/AU OR "LARSEN B DUE"/AU OR "LARSEN B H"/AU OR "LARSEN B HVOLBAEK"/AU OR "LARSEN B K"/AU OR "LARSEN B L"/AU OR "LARSEN B M"/AU OR "LARSEN B R"/AU OR "LARSEN B RICHTER"/AU OR "LARSEN B RIIS"/AU OR "LARSEN B S"/AU OR "LARSEN B T"/AU OR "LARSEN B V"/AU OR "LARSEN BJARNE"/AU OR "LARSEN BJARNE D"/AU OR "LARSEN BJARNE DUE"/AU OR "LARSEN BJARNE E"/AU OR "LARSEN BJARNE N"/AU OR "LARSEN BJARNE NYHOLM"/AU OR "LARSEN BJARNE RUDOLF EBBESKOV"/AU)

L47 639 SEA FILE=CAPLUS ABB=ON PLU=ON ("PETERSEN J"/AU OR "PETERSEN J A"/AU OR "PETERSEN J A K"/AU OR "PETERSEN J B"/AU OR "PETERSEN J B B"/AU OR "PETERSEN J BRAMMER"/AU OR "PETERSEN J C"/AU OR "PETERSEN J CLAINE"/AU OR "PETERSEN J D"/AU OR "PETERSEN J F"/AU OR "PETERSEN J F W"/AU OR "PETERSEN J G L"/AU OR "PETERSEN J G LITSKE"/AU OR "PETERSEN J H"/AU OR "PETERSEN J J"/AU OR "PETERSEN J KAAS"/AU OR "PETERSEN J L"/AU OR "PETERSEN J L W"/AU OR "PETERSEN J LYNG"/AU OR "PETERSEN J M"/AU OR "PETERSEN J N"/AU OR "PETERSEN J O"/AU OR "PETERSEN J OTZEN"/AU OR "PETERSEN J R"/AU OR "PETERSEN J RAAGAARD"/AU OR "PETERSEN J RGEN"/AU OR "PETERSEN J ROED"/AU OR "PETERSEN J S"/AU OR "PETERSEN J STYHR"/AU OR "PETERSEN J U H"/AU OR "PETERSEN J V"/AU OR "PETERSEN J W"/AU OR "PETERSEN J WESTPHAL"/AU OR "PETERSEN J WULFF"/AU OR "PETERSEN JORGEN"/AU OR "PETERSEN JORGEN B"/AU OR "PETERSEN JORGEN F"/AU OR "PETERSEN JORGEN H"/AU OR "PETERSEN JORGEN HOLM"/AU OR "PETERSEN JORGEN LORENZO"/AU OR "PETERSEN JORGEN S"/AU OR "PETERSEN JORGEN SOBERG"/AU OR "PETERSEN JORGEN SOEBERG"/AU)

L48 119 SEA FILE=CAPLUS ABB=ON PLU=ON ("MEIER E"/AU OR "MEIER E A"/AU OR "MEIER E F"/AU OR "MEIER E G"/AU OR "MEIER E J J"/AU OR "MEIER E M M"/AU OR "MEIER E P"/AU OR "MEIER E V"/AU OR "MEIER EDDI"/AU OR "MEIER EDDIE"/AU)

L49 9 SEA FILE=CAPLUS ABB=ON PLU=ON ("KJOLBYE ANNE"/AU OR "KJOLBYE ANNE LOUISE"/AU)

L50 79 SEA FILE=CAPLUS ABB=ON PLU=ON ("JORGENSEN N"/AU OR "JORGENSEN

N A"/AU OR "JORGENSEN N E"/AU OR "JORGENSEN N O"/AU OR  
 "JORGENSEN N O G"/AU OR "JORGENSEN N P"/AU OR "JORGENSEN N  
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L51 781 SEA FILE=CAPLUS ABB=ON PLU=ON ("NIELSEN M"/AU OR "NIELSEN M  
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 "NIELSEN MORTEN T"/AU OR "NIELSEN MORTEN THELLEFSEN"/AU OR  
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L52 80 SEA FILE=CAPLUS ABB=ON PLU=ON ("HOLSTEIN RATHLOU N H"/AU OR  
 "HOLSTEIN RATHLOU N H N H"/AU OR "HOLSTEIN RATHLOU NIELS H"/AU  
 OR "HOLSTEIN RATHLOU NIELS HENRIK"/AU)

L53 379 SEA FILE=CAPLUS ABB=ON PLU=ON ("MARTINS J"/AU OR "MARTINS J  
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 "MARTINS J B"/AU OR "MARTINS J B L"/AU OR "MARTINS J BENUZZI"/A  
 U OR "MARTINS J C"/AU OR "MARTINS J C A"/AU OR "MARTINS J C  
 F"/AU OR "MARTINS J D"/AU OR "MARTINS J E C"/AU OR "MARTINS J  
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 OR "MARTINS J K"/AU OR "MARTINS J L"/AU OR "MARTINS J L  
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 OR "MARTINS J MANUEL LEAO"/AU OR "MARTINS J MARTIN"/AU OR  
 "MARTINS J O"/AU OR "MARTINS J P"/AU OR "MARTINS J P S"/AU OR  
 "MARTINS J R"/AU OR "MARTINS J R M"/AU OR "MARTINS J S"/AU OR  
 "MARTINS J S S"/AU OR "MARTINS J S SA"/AU OR "MARTINS J V"/AU  
 OR "MARTINS J V C"/AU OR "MARTINS J VANDERLEI"/AU OR "MARTINS  
 JAMES"/AU OR "MARTINS JAMES B"/AU)

L54 2371 SEA FILE=CAPLUS ABB=ON PLU=ON (L46 OR L47 OR L48 OR L49 OR  
 L50 OR L51 OR L52 OR L53)

L55 29 SEA FILE=CAPLUS ABB=ON PLU=ON L54 AND ?INTERCELL?

L56 20 SEA FILE=CAPLUS ABB=ON PLU=ON L55 AND ?COMMUN?

=> d l56 ibib abs tot

L56 ANSWER 1 OF 20 CAPLUS COPYRIGHT 2007 ACS on STN  
 ACCESSION NUMBER: 2007:888184 CAPLUS Full-text  
 TITLE: A model of smooth muscle cell synchronization in the  
 arterial wall  
 AUTHOR(S): Jacobsen, Jens Christian Brings; Aalkjaer, Christian;  
 Nilsson, Holger; Matchkov, Vladimir V.; Freiberg,  
 Jacob; Holstein-Rathlou, Niels-Henrik  
 CORPORATE SOURCE: Biomedical Institute, University of Copenhagen,  
 Copenhagen, Den.

SOURCE: American Journal of Physiology (2007), 293(1, Pt. 2),  
H229-H237  
CODEN: AJPHAP; ISSN: 0002-9513  
PUBLISHER: American Physiological Society  
DOCUMENT TYPE: Journal  
LANGUAGE: English

AB Vasomotion is a rhythmic variation in microvascular diameter. Although known for more than 150 years, the cellular processes underlying the initiation of vasomotion are not fully understood. In the present study, a model of a single cell is extended by coupling a number of cells into a tube. The simulated results point to a permissive role of cGMP in establishing intercellular synchronization. In sufficient concentration, cGMP may activate a cGMP-sensitive calcium-dependent chloride channel, causing a tight spatiotemporal coupling between release of sarcoplasmic reticulum calcium, membrane depolarization, and influx of extracellular calcium. Low [cGMP] is associated only with unsynchronized waves. At intermediate concns., cells display either waves or whole cell oscillations, but these remain unsynchronized between cells. Whole cell oscillations are associated with rhythmic variation in membrane potential and flow of current through gap junctions. The amplitude of these oscillations in potential grows with increasing [cGMP], and, past a certain threshold, they become strong enough to entrain all cells in the vascular wall, thereby initiating sustained vasomotion. In this state there is a rhythmic flow of calcium through voltage-sensitive calcium channels into the cytoplasm, making the frequency of established vasomotion sensitive to membrane potential. It is concluded that elec. coupling through gap junctions is likely to be responsible for the rapid synchronization across a large number of cells. Gap junctional current between cells is due to the appearance of oscillations in the membrane potential that again depends on the entrainment of sarcoplasmic reticulum and plasma membrane within the individual cell.

REFERENCE COUNT: 49 THERE ARE 49 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L56 ANSWER 2 OF 20 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2007:883803 CAPLUS Full-text

TITLE: Discovery of potent gap-junction modifiers as novel antiarrhythmic agents: From stable hexa-peptides to orally available small molecules

AUTHOR(S): Butera, John A.; Larsen, Bjarne Due; Kerns, Edward; Di, Li; Hennan, James K.; Swillo, Robert; Morgan, Gwen; Huselton, Christine; Unwalla, Ray J.; Petersen, J-rgen

CORPORATE SOURCE: Chemical & Screening Sciences, Wyeth Research, Princeton, NJ, Princeton, NJ, 08543, USA

SOURCE: Abstracts of Papers, 234th ACS National Meeting, Boston, MA, United States, August 19-23, 2007 (2007), MEDI-450. American Chemical Society: Washington, D. C.

CODEN: 69JNR2

DOCUMENT TYPE: Conference; Meeting Abstract; (computer optical disk)

LANGUAGE: English

AB Ventricular and atrial arrhythmias contribute significantly to overall morbidity and mortality in the developed world. Uncontrolled ventricular tachycardia (VT) can quickly cascade to ventricular fibrillation (VF) and then to sudden cardiac death. While less likely to induce sudden death, atrial fibrillation (AF) is a more prevalent form of cardiac arrhythmia which is associated with palpitations, dizziness, angina, hemodynamic impairment, and an increased risk of stroke. Pivotal failed clin. studies have illustrated the unmet medical need to discover safer and more efficacious antiarrhythmic agents. Impaired gap-junction intracellular communication has been implicated



as an underlying mechanism for the propagation of unorganized cardiac elec. signals. Rotigaptide, a novel, stable hexapeptide shown to re-establish gap-junctional intercellular communication, is a first-in-class mol. being developed for the prevention (iv) of VT/VF. This presentation will review its discovery and its in vitro and in vivo characterization as a potent and efficacious antiarrhythmic agent. SAR from the hexapeptide series coupled with pharmaceutical profiling and focused screen of an internal small peptide library led to the identification and characterization of several structural classes of orally active small mol. gap-junction modifiers possessing remarkable stability and potency. The second half of the talk will focus on the characterization of these leads as potential agents to treat chronic arrhythmias such as AF.

L56 ANSWER 3 OF 20 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2006:341561 CAPLUS Full-text

DOCUMENT NUMBER: 144:381710

TITLE: Rotigaptide (ZP123) prevents spontaneous ventricular arrhythmias and reduces infarct size during myocardial ischemia/reperfusion injury in open-chest dogs

AUTHOR(S): Hennan, James K.; Swillo, Robert E.; Morgan, Gwen A.; Keith, James C., Jr.; Schaub, Robert G.; Smith, Robert P.; Feldman, Hal S.; Haugan, Ketil; Kantrowitz, Joel; Wang, Phil J.; Abu-Qare, Aqel; Butera, John; Larsen, Bjarne D.; Crandall, David L.

CORPORATE SOURCE: Cardiovascular and Metabolic Disease Research, Wyeth Research, Collegeville, PA, USA

SOURCE: Journal of Pharmacology and Experimental Therapeutics (2006), 317(1), 236-243

CODEN: JPETAB; ISSN: 0022-3565

PUBLISHER: American Society for Pharmacology and Experimental Therapeutics

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The antiarrhythmic and cardioprotective effect of increasing gap junction intercellular communication during ischemia/reperfusion injury has not been studied. The antiarrhythmic peptide rotigaptide (previously ZP123), which maintains gap junction intercellular communication, was tested in dogs subjected to a 60-min coronary artery occlusion and 4 h of reperfusion. Rotigaptide was administered i.v. 10 min before reperfusion as a bolus + i.v. infusion at doses of 1 ng/kg bolus + 10 ng/kg/h infusion (n = 6), 10 ng/kg bolus + 100 ng/kg/h infusion (n = 5), 100 ng/kg bolus + 1000 ng/kg/h infusion (n = 8), 1000 ng/kg bolus + 10 µg/kg/h infusion (n = 6), and vehicle control (n = 5). Premature ventricular complexes (PVCs) were quantified during reperfusion. A series of four or more consecutive PVCs was defined as ventricular tachycardia (VT). The total incidence of VT was reduced significantly with the two highest doses of rotigaptide ( $20.3 \pm 10.9$  and  $4.3 \pm 4.1$  events;  $p < 0.05$ ) compared with controls ( $48.7 \pm 6.0$ ). Total PVCs were reduced significantly from  $25.1 \pm 4.2\%$  in control animals to  $11.0 \pm 4.4$  and  $1.7 \pm 1.3\%$  after the two highest doses of rotigaptide. Infarct size, expressed as a percentage of the left ventricle, was reduced significantly from  $13.2 \pm 1.9$  in controls to  $7.1 \pm 1.0$  ( $p < 0.05$ ) at the highest dose of rotigaptide. Ultrastructural evaluation revealed no differences in myocardial injury in the infarct area, area at risk, border zone, or normal zone in vehicle and rotigaptide-treated animals. However, rotigaptide did increase the presence of gap junctions in the area at risk ( $p = 0.022$ , Fisher's exact test). Rotigaptide had no effect on heart rate, blood pressure, heart rate-corrected QT interval, or left ventricular end-diastolic pressure. In conclusion, these results demonstrate that rotigaptide is a potent antiarrhythmic compound with cardioprotective effects and desirable safety.

REFERENCE COUNT: 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS  
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L56 ANSWER 4 OF 20 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2006:317741 CAPLUS Full-text

DOCUMENT NUMBER: 145:4711

TITLE: The predominant mechanism of intercellular  
calcium wave propagation changes during long-term  
culture of human osteoblast-like cells

AUTHOR(S): Henriksen, Zanne; Hiken, Jeffrey F.; Steinberg, Thomas  
H.; Jorgensen, Niklas R.

CORPORATE SOURCE: Osteoporosis and Bone Metabolic Unit, Dept. 545,  
Departments of Endocrinology and Clinical  
Biochemistry, Copenhagen University Hospital Hvidovre,  
Hvidovre, DK-2650, Den.

SOURCE: Cell Calcium (2006), 39(5), 435-444

CODEN: CECADV; ISSN: 0143-4160

PUBLISHER: Elsevier

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Intercellular calcium waves (ICW) are calcium transients that spread from cell  
to cell in response to different stimuli. The authors previously demonstrated  
that human osteoblast-like cells in culture propagate ICW in response to mech.  
stimulation by 2 mechanisms. One mechanism involves autocrine activation of  
P2Y receptors, and the other requires gap junctional communication. In the  
current work the authors ask whether long-term culture of osteoblast-like  
cells affects the propagation of ICW by these 2 mechanisms. Human osteoblast-  
like cells were isolated from bone marrow. Mech. induced ICW were assessed by  
video imaging of Fura-2 loaded cells after 1, 2 and 4 mo culture. The P2Y2  
receptor and the gap junction protein Cx43 were assessed by Western blot and  
real-time PCR. In resting conditions, P2Y mediated ICW prevailed and spread  
rapidly to about 13 cells. P2Y receptor desensitization by ATP disclosed gap  
junction-mediated ICW which diffused more slowly and involved not more than 5  
to 6 cells. After 2 mo in culture, ICW appeared slower and wave propagation  
was much less inhibited by P2Y desensitization, suggesting an increase in gap  
junction-mediated ICW. After 4 mo in culture cells still responded to addition  
of ATP, but P2Y desensitization did not inhibit ICW propagation. The authors'  
data indicate that the relative role of P2Y-mediated and gap junction-mediated  
ICW changes during osteoblast differentiation in vitro. In less  
differentiated cells, P2Y-mediated ICW predominate, but as cells differentiate  
in culture, gap-junction-mediated ICW become more prominent. These results  
suggest that P2Y receptor-mediated and gap junction-mediated mechanisms of  
intercellular calcium signaling may play different roles during  
differentiation of bone-forming cells.

REFERENCE COUNT: 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS  
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L56 ANSWER 5 OF 20 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2006:242808 CAPLUS Full-text

DOCUMENT NUMBER: 145:241309

TITLE: Rotigaptide (ZP123) Reverts Established Atrial  
Conduction Velocity Slowing

AUTHOR(S): Haugan, Ketil; Kjolbye, Anne Louise; Hennan,  
James K.; Petersen, Jorgen Soberg

CORPORATE SOURCE: Zealand Pharma A/S, Glostrup, DK-2600, Den.

SOURCE: Cell Communication & Adhesion (2005), 12(5-6), 271-278

CODEN: CCAEBH; ISSN: 1541-9061

PUBLISHER: Taylor & Francis, Inc.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Rotigaptide (ZP123) increases gap junction intercellular communication (GJIC) and prevents stress-induced cardiac conduction velocity (CV) slowing. However, the effect of rotigaptide on established cardiac conduction slowing and the duration of effect on rotigaptide during washout is unknown. Metabolic stress (induced by superfusion with nonoxygenated glucose-free Tyrodes buffer) was associated with a 30% decrease in atrial CV in vehicle-treated rat atria. Rotigaptide treatment initiated after a period of 30 min of metabolic stress produced a rapid and significant increase in CV compared to vehicle-treated time controls. During washout of rotigaptide for 30 min (while subjected to metabolic stress), there was a minor decrease in atrial CV; however, this was not significantly different from atrial CV in a rotigaptide-treated time control group. Rotigaptide treatment rapidly normalizes established conduction slowing in atria subjected to metabolic stress. However, the cessation of effect was considerably slower than the onset of action.

REFERENCE COUNT: 16 THERE ARE 16 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L56 ANSWER 6 OF 20 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2006:204533 CAPLUS Full-text

DOCUMENT NUMBER: 144:343331

TITLE: The antiarrhythmic peptide rotigaptide (ZP123) increases gap junction intercellular communication in cardiac myocytes and HeLa cells expressing connexin 43

AUTHOR(S): Clarke, Thomas C.; Thomas, Dafydd; Petersen, Jorgen S.; Evans, W. Howard; Martin, Patricia E. M.

CORPORATE SOURCE: Department of Medical Biochemistry and Immunology & Wales Heart Research Institute, Cardiff University, Cardiff, UK

SOURCE: British Journal of Pharmacology (2006), 147(5), 486-495

CODEN: BJPCBM; ISSN: 0007-1188

PUBLISHER: Nature Publishing Group

DOCUMENT TYPE: Journal

LANGUAGE: English

AB We investigated the effects of rotigaptide (ZP123), a stable hexapeptide with antiarrhythmic properties, on gap junction mediated intercellular communication in contracting rat neonatal cardiac myocytes, HL-1 cells derived from cardiac atrium and in HeLa cells transfected with cDNA encoding Cx43-GFP, Cx32-GFP, Cx26-GFP, wild-type Cx43 or wild-type Cx26. Intercellular communication was monitored before and after treatment with rotigaptide following microinjection of small fluorescent dyes (MW<1 kDa). The communication-modifying effect of rotigaptide was confined to cells expressing Cx43 since the peptide had no effect on dye transfer in HeLa cells expressing Cx32-GFP, Cx26-GFP or wild-type Cx26. In contrast, HeLa cells expressing Cx43-GFP exposed to 50 nM rotigaptide for 5 h showed a 40% increase in gap junction mediated communication. Rotigaptide (50 nM) increased intercellular dye transfer in myocytes and atrial HL-1 cells, where Cx43 is the dominant connexin. However, it caused no change in cell beating rates of cardiac myocytes and Western blot anal. showed that rotigaptide did not modify the overall level of Cx43 expression and changes in the phosphorylation status of the protein were not observed. We conclude that the effects of rotigaptide were confined to cells expressing Cx43.

REFERENCE COUNT: 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L56 ANSWER 7 OF 20 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2006:169413 CAPLUS Full-text

DOCUMENT NUMBER: 144:324502  
 TITLE: Treatment With the Gap Junction Modifier Rotigaptide (ZP123) Reduces Infarct Size in Rats With Chronic Myocardial Infarction  
 AUTHOR(S): Haugan, Ketil; Marcussen, Niels; Kjolbye, Anne Louise; Nielsen, Morten Schak; Hennan, James K.; Petersen, Jorgen Soberg  
 CORPORATE SOURCE: Department of Pharmacology, Zealand Pharma A/S, Glostrup, Den.  
 SOURCE: Journal of Cardiovascular Pharmacology (2006), 47(2), 236-242  
 CODEN: JCPCDT; ISSN: 0160-2446  
 PUBLISHER: Lippincott Williams & Wilkins  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English

AB Treatment with non-selective drugs (eg, long-chain alcs., halothane) that reduce gap junction intercellular communication (GJIC) is associated with reduced infarct size after myocardial infarction (MI). Therefore, it has been suggested that gap junction intercellular communication stimulating compds. may increase infarct size. The antiarrhythmic peptide analog rotigaptide (ZP123) increases cardiac gap junction intercellular communication and the purpose of the present study was to examine the effects of rotigaptide treatment on infarct size. Myocardial infarction was induced in male rats by ligation of the left anterior descending artery (LAD). Rats (n = 156) were treated with rotigaptide at three dose levels or vehicle from the onset of ischemia and for 3 wk following LAD occlusion. Infarct size was determined using histomorphometry after 3 wk treatment. Rotigaptide treatment producing steady state plasma levels of  $0.8 \pm 0.1$ ,  $5.5 \pm 0.5$ , and  $86 \pm 8$  nmol/L had no effect on mortality, but reduced infarct size to  $90 \pm 10\%$  ( $P = 0.41$ ),  $67 \pm 7\%$  ( $P = 0.005$ ), and  $82 \pm 7\%$  ( $P = 0.13$ ), resp. relative to vehicle-treated myocardial infarction rats ( $100 \pm 12\%$ ). In contrast to what was predicted, our data demonstrates that rotigaptide treatment was associated with a significant infarct size reduction. We conclude that whereas treatment with non-selective inhibitors of gap junction intercellular communication cause a reduction in infarct size, this information cannot be extrapolated to the effects of compds. that selectively increase gap junction intercellular communication.

REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L56 ANSWER 8 OF 20 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2005:1159817 CAPLUS Full-text  
 DOCUMENT NUMBER: 143:399761  
 TITLE: The antiarrhythmic peptide analog rotigaptide (ZP123) stimulates gap junction intercellular communication in human osteoblasts and prevents decrease in femoral trabecular bone strength in ovariectomized rats  
 AUTHOR(S): Joergensen, Niklas Rye; Teilmann, Stefan Cuoni; Henriksen, Zanne; Meier, Eddi; Hansen, Susanne Syberg; Jensen, Jens-Erik Beck; Soerensen, Ole Helmer; Petersen, Joergen Soeberg  
 CORPORATE SOURCE: The Osteoporosis and Metabolic Bone Unit, Department of Endocrinology and Clinical Biochemistry, Copenhagen University Hospital H:S, Hvidovre, DK-2650, Den.  
 SOURCE: Endocrinology (2005), 146(11), 4745-4754  
 CODEN: ENDOAO; ISSN: 0013-7227  
 PUBLISHER: Endocrine Society  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English

AB Gap junctions play an important role in bone development and function, but the lack of pharmacol. tools has hampered the gap junction research. The antiarrhythmic peptides stimulate gap junction communication between cardiomyocytes, but effects in noncardiac tissue are unknown. The purpose of this study was to examine whether antiarrhythmic peptides, which are small peptides increasing gap junctional conductivity, show specific binding to osteoblasts and investigate the effect of the stable analog rotigaptide (ZP 123) on gap junctional intercellular communication in vitro and on bone mass and strength in vivo. Cell coupling and calcium signaling were assessed in vitro on human, primary, osteoblastic cells. In vivo effects of rotigaptide on bone strength and d. were determined 4 wk after ovariectomy in rats treated with either vehicle, s.c. injection twice daily (300 nmol/kg) or by continuous i.p. infusion (158 nmol/kg/day). During metabolic stress, a high affinity-binding site ( $KD = 0.1$  nM) with low d. (15 fmol/mg protein) for [ $^{125}I$ ]di-I-AAP 10 was demonstrated. During physiol. conditions, specific binding sites for [ $^{125}I$ ]AAP 10 could not be shown. Studies of the effects of rotigaptide on propagation of intercellular calcium waves and cell-to-cell coupling demonstrated that 10 nM rotigaptide produced a small increase in intercellular communication during physiol. conditions (+4.5% vs. vehicle). During conditions with metabolic stress, 10 nM rotigaptide produced an increase in coupling measured by both methods. Four weeks after ovariectomy, bone strength of the femoral head was reduced by 20% in vehicle-treated ovariectomized rats, which was completely prevented in both rotigaptide-treated groups. Rotigaptide also prevented decreases in bone mineral. We conclude that the stable analog rotigaptide increases gap junctional communication in osteoblasts in vitro and preferably during conditions with metabolic stress. Rotigaptide further prevents ovariectomy-induced bone loss in vivo. Thus, gap junction modulation may be a promising new target for osteoporosis therapy.

REFERENCE COUNT: 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L56 ANSWER 9 OF 20 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2005:153560 CAPLUS Full-text

DOCUMENT NUMBER: 142:273740

TITLE: Pharmacological stimulation of cardiac gap junction coupling does not affect ischemia-induced focal ventricular tachycardia or triggered activity in dogs

AUTHOR(S): King, Dezhi; Kjolbye, Anne Louise; Petersen, Jorgen S.; Martins, James B.

CORPORATE SOURCE: Department of Internal Medicine, Carver College of Medicine, University of Iowa, Iowa City, IA, USA

SOURCE: American Journal of Physiology (2005), 288(2, Pt. 2), H511-H516

CODEN: AJPHAP; ISSN: 0002-9513

PUBLISHER: American Physiological Society

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The role of gap junction intercellular communication (GJIC) in ischemia-induced focal ventricular tachycardia (VT) is unknown. The authors have developed a new, stable antiarrhythmic peptide analog named ZP123 that selectively increases GJIC and prevents reentrant VT. Our aim in this study was to use ZP123 as a tool to assess the role of GJIC on occurrence of ischemia-induced focal VT and triggered activity (TA) due to delayed afterdepolarizations (DADs). Focal VT was induced by programmed stimulation in  $\alpha$ -chloralose-anesthetized, open-chest dogs 1-4 h after coronary artery occlusion. Three-dimensional activation mapping was done using 6 bipolar electrograms on each of 23 multipolar needles in the risk zone. Dogs were randomly assigned to receive either saline or ZP123 cumulatively at three dose levels (an i.v. bolus followed by a 30-min infusion per dose). Attempts to

induce VT were repeated in each dose. Mass spectrometry was used to measure plasma ZP123 concns. Standard microelectrode techniques were used for in vitro study of DADs and TA. Twenty-six dogs with focal VT were included. ZP123 did not affect the inducibility of focal VT at any plasma concns. vs. saline ( $0.8 \pm 0.1$  nM, 77 vs. 75%;  $7.8 \pm 0.4$  nM, 86 vs. 77%; and  $78.8 \pm 5.0$  nM, 77 vs. 91%). In vitro, ZP123 did not affect the induction of DADs (12/12) and TAs (10/10) in ischemic tissues or tissue removed from the origin of focal VT (DADs, 8/8; TAs, 4/4). Therefore, although indirect, the data with the doses and concns. used suggest that GJIC may not play a major role in the genesis of focal activity in the ischemic models studied.

REFERENCE COUNT: 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L56 ANSWER 10 OF 20 CAPLUS COPYRIGHT 2007 ACS on STN  
 ACCESSION NUMBER: 2004:467909 CAPLUS Full-text  
 DOCUMENT NUMBER: 141:33831  
 TITLE: Peptide gap junction modulators, and therapeutic use thereof  
 INVENTOR(S): Larsen, Bjarne Due; Knudsen, Carsten Boye; Petersen, Jorgen Soberg  
 PATENT ASSIGNEE(S): Zealand Pharma A/S, Den.  
 SOURCE: PCT Int. Appl., 71 pp.  
 CODEN: PIXXD2  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 1  
 PATENT INFORMATION:

| PATENT NO.             | KIND                                                                                                                                                                                                                                                                                                                                                                                       | DATE     | APPLICATION NO.  | DATE       |
|------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------|------------------|------------|
| WO 2004048400          | A1                                                                                                                                                                                                                                                                                                                                                                                         | 20040610 | WO 2003-DK805    | 20031125   |
| W:                     | AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW |          |                  |            |
| RW:                    | BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG                                                                                                                         |          |                  |            |
| CA 2506490             | A1                                                                                                                                                                                                                                                                                                                                                                                         | 20040610 | CA 2003-2506490  | 20031125   |
| AU 2003281986          | A1                                                                                                                                                                                                                                                                                                                                                                                         | 20040618 | AU 2003-281986   | 20031125   |
| EP 1569953             | A1                                                                                                                                                                                                                                                                                                                                                                                         | 20050907 | EP 2003-773592   | 20031125   |
| R:                     | AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK                                                                                                                                                                                                                                                                 |          |                  |            |
| BR 2003016488          | A                                                                                                                                                                                                                                                                                                                                                                                          | 20051011 | BR 2003-16488    | 20031125   |
| CN 1717415             | A                                                                                                                                                                                                                                                                                                                                                                                          | 20060104 | CN 2003-80104091 | 20031125   |
| ZA 2005003600          | A                                                                                                                                                                                                                                                                                                                                                                                          | 20060830 | ZA 2005-3600     | 20031125   |
| JP 2006524182          | T                                                                                                                                                                                                                                                                                                                                                                                          | 20061026 | JP 2004-554243   | 20031125   |
| NZ 540155              | A                                                                                                                                                                                                                                                                                                                                                                                          | 20061130 | NZ 2003-540155   | 20031125   |
| IN 2005DN01974         | A                                                                                                                                                                                                                                                                                                                                                                                          | 20070119 | IN 2005-DN1974   | 20050510   |
| MX 2005PA05444         | A                                                                                                                                                                                                                                                                                                                                                                                          | 20050930 | MX 2005-PA5444   | 20050520   |
| NO 2005003053          | A                                                                                                                                                                                                                                                                                                                                                                                          | 20050621 | NO 2005-3053     | 20050621   |
| US 2006194947          | A1                                                                                                                                                                                                                                                                                                                                                                                         | 20060831 | US 2006-534201   | 20060407   |
| PRIORITY APPLN. INFO.: |                                                                                                                                                                                                                                                                                                                                                                                            |          | US 2002-428973P  | P 20021125 |
|                        |                                                                                                                                                                                                                                                                                                                                                                                            |          | WO 2003-DK805    | W 20031125 |

OTHER SOURCE(S): MARPAT 141:33831

AB Dipeptides are disclosed that facilitate the intercellular communication mediated by gap junctions. The invention has a wide spectrum of useful

applications including use in the treatment of diseases associated with impaired gap junction intracellular communication. Peptide preparation is also described.

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L56 ANSWER 11 OF 20 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2003:159138 CAPLUS Full-text

DOCUMENT NUMBER: 139:50541

TITLE: Expression of connexin 37, 40 and 43 in rat mesenteric arterioles and resistance arteries

AUTHOR(S): Gustafsson, Finn; Mikkelsen, Hanne B.; Arensbak, Birgitte; Thuneberg, Lars; Neve, Soren; Jensen, Lars J.; Holstein-Rathlou, Niels-Henrik

CORPORATE SOURCE: The Panum Institute, Division of Renal and Cardiovascular Physiology, Department of Medical Physiology, University of Copenhagen, Copenhagen, 2200, Den.

SOURCE: Histochemistry and Cell Biology (2003), 119(2), 139-148

CODEN: HCBIFP; ISSN: 0948-6143

PUBLISHER: Springer-Verlag

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Connexins are the protein constituents of gap junctions which mediate intercellular communication in most tissues. In arterioles gap junctions appear to be important for conduction of vasomotor responses along the vessel. Studies of the expression pattern of connexin isoforms in the microcirculation are sparse. We investigated the expression of the three major vascular connexins in mesenteric arterioles (diameter <50  $\mu$ m) from male Sprague-Dawley rats, since conducted vasomotor responses have been described in these vessels. The findings were compared with those obtained from upstream small resistance arteries. Indirect immunofluorescence techniques were used on whole mounts of mesenteric arterioles and on frozen sections of resistance arteries (diameter approx. 300  $\mu$ m). Mesenteric arterioles expressed Cx40 and Cx43 in the endothelial layer, and Cx37 was found in most but not all vessels. Connexins were not demonstrated in the media. In resistance arteries endothelial cells expressed Cx37, Cx40 and Cx43. Ultrastructural studies of mesenteric arterioles confirmed that gap junction plaques between endothelial cells are present, whereas myoendothelial, or smooth muscle cell gap junctions could not be demonstrated. The findings suggest that smooth muscle cells in mesenteric arterioles may not be well coupled and favor that conducted vasomotor responses in these vessels are propagated through the endothelial cell layer.

REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L56 ANSWER 12 OF 20 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2003:82823 CAPLUS Full-text

DOCUMENT NUMBER: 139:33876

TITLE: Activation of L-type Calcium Channels Is Required for Gap Junction-mediated Intercellular Calcium Signaling in Osteoblastic Cells

AUTHOR(S): Jorgensen, Niklas Rye; Teilmann, Stefan Cuoni; Henriksen, Zanne; Civitelli, Roberto; Sorensen, Ole Helmer; Steinberg, Thomas H.

CORPORATE SOURCE: Copenhagen University Hospitals, Department of Endocrinology, Osteoporosis and Metabolic Bone Unit, Copenhagen Hospital Corporation, Hvidovre, DK-2650, Den.

SOURCE: Journal of Biological Chemistry (2003), 278(6),  
4082-4086  
CODEN: JBCHA3; ISSN: 0021-9258  
PUBLISHER: American Society for Biochemistry and Molecular  
Biology  
DOCUMENT TYPE: Journal  
LANGUAGE: English

AB The propagation of mech. induced intercellular calcium waves (ICW) among osteoblastic cells occurs both by activation of P2Y (purinergic) receptors by extracellular nucleotides, resulting in "fast" ICW, and by gap junctional communication in cells that express connexin43 (Cx43), resulting in "slow" ICW. Human osteoblastic cells transmit intercellular calcium signals by both of these mechanisms. In the current studies we have examined the mechanism of slow gap junction-dependent ICW in osteoblastic cells. In ROS rat osteoblastic cells, gap junction-dependent ICW were inhibited by removal of extracellular calcium, plasma membrane depolarization by high extracellular potassium, and the L-type voltage-operated calcium channel inhibitor, nifedipine. In contrast, all these treatments enhanced the spread of P2 receptor-mediated ICW in UMR rat osteoblastic cells. Using UMR cells transfected to express Cx43 (UMR/Cx43) we confirmed that nifedipine sensitivity of ICW required Cx43 expression. In human osteoblastic cells, gap junction-dependent ICW also required activation of L-type calcium channels and influx of extracellular calcium.

REFERENCE COUNT: 15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L56 ANSWER 13 OF 20 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2002:973444 CAPLUS Full-text

DOCUMENT NUMBER: 139:227633

TITLE: Intercellular junctions and cell-cell  
communication in bone

AUTHOR(S): Civitelli, Roberto; Lecanda, Fernando; Jorgensen,  
Niklas R.; Steinberg, Thomas H.

CORPORATE SOURCE: Departments of Medicine and Cell Biology and  
Physiology, Division of Bone and Mineral Diseases,  
Washington University School of Medicine and  
Barnes-Jewish Hospital, St. Louis, MO, 63110, USA

SOURCE: Principles of Bone Biology (2nd Edition) (2002),  
Volume 1, 287-302. Editor(s): Bilezikian, John P.;  
Raisz, Lawrence G.; Rodan, Gideon A. Academic Press:  
San Diego, Calif.

CODEN: 69DJZ2; ISBN: 0-12-098652-3

DOCUMENT TYPE: Conference; General Review

LANGUAGE: English

AB A review of the current knowledge about the role of direct cell-cell interactions in the development and remodeling of the skeletal tissue, focusing on cell-cell adhesion via cadherins and other cell adhesion mols., cell-cell communication via gap junctions, and short-range calcium signals, or calcium waves.

REFERENCE COUNT: 154 THERE ARE 154 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L56 ANSWER 14 OF 20 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2002:754415 CAPLUS Full-text

DOCUMENT NUMBER: 137:263304

TITLE: Synthesis of peptides and medical uses of  
intracellular communication facilitating  
compounds

INVENTOR(S): Larsen, Bjarne Due; Petersen, Jorgen



Soberg; Meier, Eddie; Kjolbye,  
 Anne Louise; Jorgensen, Niklas Rye;  
 Nielsen, Morten Schak; Holstein-Rathlou,  
 Niels-Henrik; Martins, James B.

PATENT ASSIGNEE(S): Zealand Pharmaceuticals A/S, Den.

SOURCE: PCT Int. Appl., 233 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 2

PATENT INFORMATION:

| PATENT NO.                                                                                                                                                                                                                                                                                                                                                            | KIND | DATE     | APPLICATION NO. | DATE       |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------|----------|-----------------|------------|
| WO 2002077017                                                                                                                                                                                                                                                                                                                                                         | A2   | 20021003 | WO 2002-US5773  | 20020222   |
| WO 2002077017                                                                                                                                                                                                                                                                                                                                                         | A3   | 20031009 |                 |            |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW |      |          |                 |            |
| RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG                                                                                                                                |      |          |                 |            |
| WO 2001062775                                                                                                                                                                                                                                                                                                                                                         | A2   | 20010830 | WO 2001-DK127   | 20010222   |
| WO 2001062775                                                                                                                                                                                                                                                                                                                                                         | A3   | 20020131 |                 |            |
| W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW                                         |      |          |                 |            |
| RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG                                                                                                                                                                            |      |          |                 |            |
| US 2003092609                                                                                                                                                                                                                                                                                                                                                         | A1   | 20030515 | US 2001-792286  | 20010222   |
| US 7250397                                                                                                                                                                                                                                                                                                                                                            | B2   | 20070731 |                 |            |
| CA 2439101                                                                                                                                                                                                                                                                                                                                                            | A1   | 20021003 | CA 2002-2439101 | 20020222   |
| AU 2002254033                                                                                                                                                                                                                                                                                                                                                         | A1   | 20021008 | AU 2002-254033  | 20020222   |
| EP 1370276                                                                                                                                                                                                                                                                                                                                                            | A2   | 20031217 | EP 2002-723240  | 20020222   |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR                                                                                                                                                                                                                                                             |      |          |                 |            |
| JP 2005506295                                                                                                                                                                                                                                                                                                                                                         | T    | 20050303 | JP 2002-576275  | 20020222   |
| BR 2002007476                                                                                                                                                                                                                                                                                                                                                         | A    | 20060124 | BR 2002-7476    | 20020222   |
| NZ 527571                                                                                                                                                                                                                                                                                                                                                             | A    | 20070223 | NZ 2002-527571  | 20020222   |
| CN 1988914                                                                                                                                                                                                                                                                                                                                                            | A    | 20070627 | CN 2002-807402  | 20020222   |
| NO 2003003641                                                                                                                                                                                                                                                                                                                                                         | A    | 20031020 | NO 2003-3641    | 20030815   |
| MX 2003PA07537                                                                                                                                                                                                                                                                                                                                                        | A    | 20050930 | MX 2003-PA7537  | 20030821   |
| US 2005113293                                                                                                                                                                                                                                                                                                                                                         | A1   | 20050526 | US 2003-646294  | 20030822   |
| IN 2003DN01336                                                                                                                                                                                                                                                                                                                                                        | A    | 20050527 | IN 2003-DN1336  | 20030822   |
| US 2005075280                                                                                                                                                                                                                                                                                                                                                         | A1   | 20050407 | US 2004-772774  | 20040204   |
| PRIORITY APPLN. INFO.:                                                                                                                                                                                                                                                                                                                                                |      |          | US 2001-792286  | A 20010222 |
|                                                                                                                                                                                                                                                                                                                                                                       |      |          | WO 2001-DK127   | A 20010222 |
|                                                                                                                                                                                                                                                                                                                                                                       |      |          | US 2001-314470P | P 20010823 |
|                                                                                                                                                                                                                                                                                                                                                                       |      |          | DK 2000-288     | A 20000223 |
|                                                                                                                                                                                                                                                                                                                                                                       |      |          | DK 2000-738     | A 20000504 |
|                                                                                                                                                                                                                                                                                                                                                                       |      |          | US 2000-251659P | P 20001206 |
|                                                                                                                                                                                                                                                                                                                                                                       |      |          | WO 2002-US5773  | W 20020222 |

OTHER SOURCE(S): MARPAT 137:263304

AB The invention relates to novel peptides, including novel antiarrhythmic peptides of linear or cyclic structure, having improved stability in vitro and/or in vivo, to compns. comprising these peptides, and to uses of the peptides for the preparation of medicaments. The invention also relates to the use of compds. that facilitate the intercellular communication for the preparation of medicaments for the treatment of a range of diseases characterized in impaired intercellular gap junctional communication. The invention further relates to a method of treating diseases, such as bladder incontinence, disorders of alveolar tissue and bronchial tissue, impaired hearing due to diseases of the cochlea, endothelial lesions, diabetic retinopathy and diabetic neuropathy, ischemia of the central nervous system and spinal cord, dental tissue disorders including periodontal disease, kidney diseases leading to hypertension, and a method of preventing failures of bone marrow transplantation. Ac-D-Tyr-D-Pro-D-4Hyp-Gly-D-Ala-Gly-NH<sub>2</sub> (Hyp = hydroxyprolyl) was prepared by the solid-phase method and assayed for biol. activity. Graphs include those for relative cell-to-cell conductance, PI-turnover in neonatal rat cardiomyocytes, and ventricular APD<sub>90</sub> dispersion.

L56 ANSWER 15 OF 20 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2002:209645 CAPLUS Full-text

DOCUMENT NUMBER: 136:335522

TITLE: Intercellular calcium signaling occurs between human osteoblasts and osteoclasts and requires activation of osteoclast P2X<sub>7</sub> receptors

AUTHOR(S): Jorgensen, Niklas R.; Henriksen, Zanne; Sorensen, Ole H.; Eriksen, Erik F.; Civitelli, Roberto; Steinberg, Thomas H.

CORPORATE SOURCE: Osteoporosis Research Clinic, Copenhagen University Hospital, Hvidovre, DK-2650, Den.

SOURCE: Journal of Biological Chemistry (2002), 277(9), 7574-7580

CODEN: JBCHA3; ISSN: 0021-9258

PUBLISHER: American Society for Biochemistry and Molecular Biology

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Signaling between osteoblasts and osteoclasts is important in bone homeostasis. The authors previously showed that human osteoblasts propagate intercellular calcium signals via two mechanisms: autocrine activation of P2Y receptors, and gap junctional communication. In the current work the authors identified mech. induced intercellular calcium signaling between osteoblasts and osteoclasts and among osteoclasts. Intercellular calcium responses in osteoclasts required P2 receptor activation but not gap junctional communication. Pharmacol. studies and reverse transcriptase-PCR amplification demonstrated that human osteoclasts expressed functional P2Y<sub>1</sub> receptors, but, unexpectedly, desensitization of P2Y<sub>1</sub> did not block calcium signaling to osteoclasts. The authors also found that osteoclasts expressed functional P2X<sub>7</sub> receptors and showed that pharmacol. inhibition of these receptors blocked calcium signaling to osteoclasts. Thus these studies show that calcium signaling between osteoblasts and osteoclasts occurs via activation of P2 receptors, but that different families of P2 receptors are required for calcium signaling in these two cell types. Intercellular calcium signaling among bone cells is therefore amenable to pharmacol. manipulation that will specifically affect only bone-forming or bone-resorbing cells. P2 receptors may be important drug targets for the modulation of bone turnover.

REFERENCE COUNT: 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L56 ANSWER 16 OF 20 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2001:636085 CAPLUS Full-text  
 DOCUMENT NUMBER: 135:180957  
 TITLE: Preparation of novel antiarrhythmic peptides  
 INVENTOR(S): Larsen, Bjarne Due; Petersen, Jorgen  
 Soberg; Meier, Eddi; Kjolbye, Anne  
 Louise; Jorgensen, Niklas Rye;  
 Nielsen, Morten Schak; Holstein-Rathlou,  
 Niels-Henrik; Martins, James B.  
 PATENT ASSIGNEE(S): Zealand Pharmaceuticals A/S, Den.  
 SOURCE: PCT Int. Appl., 189 pp.  
 CODEN: PIXXD2  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 2  
 PATENT INFORMATION:

| PATENT NO.     | KIND                                                                                                                                                                                                                                                                                                                                                               | DATE     | APPLICATION NO. | DATE     |
|----------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------|-----------------|----------|
| WO 2001062775  | A2                                                                                                                                                                                                                                                                                                                                                                 | 20010830 | WO 2001-DK127   | 20010222 |
| WO 2001062775  | A3                                                                                                                                                                                                                                                                                                                                                                 | 20020131 |                 |          |
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| RW:            | GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG                                                                                                                                                                             |          |                 |          |
| CA 2385659     | A1                                                                                                                                                                                                                                                                                                                                                                 | 20010830 | CA 2001-2385659 | 20010222 |
| EP 1226160     | A2                                                                                                                                                                                                                                                                                                                                                                 | 20020731 | EP 2001-907393  | 20010222 |
| EP 1226160     | B1                                                                                                                                                                                                                                                                                                                                                                 | 20041215 |                 |          |
| R:             | AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR                                                                                                                                                                                                                                                             |          |                 |          |
| JP 2003528826  | T                                                                                                                                                                                                                                                                                                                                                                  | 20030930 | JP 2001-562556  | 20010222 |
| AT 284896      | T                                                                                                                                                                                                                                                                                                                                                                  | 20050115 | AT 2001-907393  | 20010222 |
| ES 2228807     | T3                                                                                                                                                                                                                                                                                                                                                                 | 20050416 | ES 2001-1907393 | 20010222 |
| PT 1226160     | T                                                                                                                                                                                                                                                                                                                                                                  | 20050429 | PT 2001-907393  | 20010222 |
| AU 781674      | B2                                                                                                                                                                                                                                                                                                                                                                 | 20050602 | AU 2001-35362   | 20010222 |
| CA 2439101     | A1                                                                                                                                                                                                                                                                                                                                                                 | 20021003 | CA 2002-2439101 | 20020222 |
| WO 2002077017  | A2                                                                                                                                                                                                                                                                                                                                                                 | 20021003 | WO 2002-US5773  | 20020222 |
| WO 2002077017  | A3                                                                                                                                                                                                                                                                                                                                                                 | 20031009 |                 |          |
| W:             | AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW |          |                 |          |
| RW:            | GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG                                                                                                                                 |          |                 |          |
| AU 2002254033  | A1                                                                                                                                                                                                                                                                                                                                                                 | 20021008 | AU 2002-254033  | 20020222 |
| EP 1370276     | A2                                                                                                                                                                                                                                                                                                                                                                 | 20031217 | EP 2002-723240  | 20020222 |
| R:             | AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR                                                                                                                                                                                                                                                             |          |                 |          |
| JP 2005506295  | T                                                                                                                                                                                                                                                                                                                                                                  | 20050303 | JP 2002-576275  | 20020222 |
| BR 2002007476  | A                                                                                                                                                                                                                                                                                                                                                                  | 20060124 | BR 2002-7476    | 20020222 |
| NZ 527571      | A                                                                                                                                                                                                                                                                                                                                                                  | 20070223 | NZ 2002-527571  | 20020222 |
| NO 2003003641  | A                                                                                                                                                                                                                                                                                                                                                                  | 20031020 | NO 2003-3641    | 20030815 |
| MX 2003PA07537 | A                                                                                                                                                                                                                                                                                                                                                                  | 20050930 | MX 2003-PA7537  | 20030821 |

|                        |    |          |                 |            |
|------------------------|----|----------|-----------------|------------|
| US 2005113293          | A1 | 20050526 | US 2003-646294  | 20030822   |
| US 2005075280          | A1 | 20050407 | US 2004-772774  | 20040204   |
| AU 2005205785          | A1 | 20050929 | AU 2005-205785  | 20050902   |
| PRIORITY APPLN. INFO.: |    |          | DK 2000-288     | A 20000223 |
|                        |    |          | DK 2000-738     | A 20000504 |
|                        |    |          | US 2000-251659P | P 20001206 |
|                        |    |          | US 2001-792286  | A 20010222 |
|                        |    |          | WO 2001-DK127   | W 20010222 |
|                        |    |          | US 2001-314470P | P 20010823 |
|                        |    |          | WO 2002-US5773  | W 20020222 |

OTHER SOURCE(S): MARPAT 135:180957

AB Peptides X-A-B-Y and cyclo(X-A-B-Y) [A and B represents chemical moieties having an amino group (radical) and a carboxy group; X represents a peptide sequence of 1 to 3 D- or L-amino acid residues or an N-terminal modification of the group A-B when Y represents a C-terminal peptide sequence of 2 to 5 D- or L-amino acid residues; X represents a peptide sequence of 2 to 5 D- or L-amino acid residues when Y represents a C-terminal peptide sequence of 1 to 3 D- or L-amino acid residues; for the linear peptide, X is optionally chemically modified at its N-terminal and has an optional linking group comprising 0-8 backbone atoms] and their mirror image or a retro analogs or pharmaceutically acceptable derivs. were prepared for treating cardiac arrhythmias. Thus, Ac-D-Tyr-D-pro-D-4Hyp-Gly- D-Ala-Gly-NH<sub>2</sub> (4Hyp = 4-hydroxyprolyl) was prepared by the solid-phase method using Tentagel-S-Ram and examined for biol. activity [assays included effect on gap junction intercellular communication (GJIC) in cardiomyocytes, binding to tissue preps. of murine heart, and effect on cAMP formation in CHO cells].

L56 ANSWER 17 OF 20 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2001:419566 CAPLUS Full-text

DOCUMENT NUMBER: 135:135043

TITLE: Expression of connexin 37, 40, and 43 mRNA and protein in renal preglomerular arterioles

AUTHOR(S): Arensbak, Birgitte; Mikkelsen, Hanne B.; Gustafsson, Finn; Christensen, Thorkil; Holstein-Rathlou, Niels-Henrik

CORPORATE SOURCE: The Panum Institute, Division of Renal and Cardiovascular Research, Department of Medical Physiology, University of Copenhagen, Blegdamsvej 3, Copenhagen N, 2200, Den.

SOURCE: Histochemistry and Cell Biology (2001), 115(6), 479-487

CODEN: HCBIFP; ISSN: 0948-6143

PUBLISHER: Springer-Verlag

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Gap junctions allow direct intercellular coupling between many cells including those in the vascular wall. Studies of connexin (Cx) expression in cells of the microcirculatory system are very few in number. However, cell-to-cell communication between cells of the arteriolar wall may be particularly important in microcirculatory control. Here, the authors investigated the expression of Cx43, Cx40, and Cx37 mRNA and proteins in primary cultures of smooth muscle cells (SMC) from rat renal preglomerular arterioles and in aorta cell line A7r5. Furthermore, protein expression in preglomerular arterioles in frozen sections was evaluated. SMC were isolated from kidneys using an iron oxide sieve method and explant technique. Total RNA from these cultures was tested by RT-PCR anal. for the expression of the 3 Cx mRNAs. Using immunofluorescence, the authors examined whether the expression pattern of Cx protein in the cell culture and frozen sections corresponded to the mRNA expression. The data showed that A7r5 and preglomerular SMC express mRNA for

Cx37 in addition to Cx43 and Cx40. In A7r5 cells, the mRNAs for Cx43, Cx40, and Cx37 were translated to protein, whereas cultured preglomerular SMC and the media of afferent arterioles in frozen sections only showed Cx40 immunoreactivity.

REFERENCE COUNT: 51 THERE ARE 51 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L56 ANSWER 18 OF 20 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2000:416277 CAPLUS Full-text

DOCUMENT NUMBER: 133:220588

TITLE: Human osteoblastic cells propagate intercellular calcium signals by two different mechanisms

AUTHOR(S): Jorgensen, Niklas R.; Henriksen, Zanne; Brot, Christine; Eriksen, Erik F.; Sorensen, Ole H.; Civitelli, Roberto; Steinberg, Thomas H.

CORPORATE SOURCE: Osteoporosis Research Center, Copenhagen, Den.

SOURCE: Journal of Bone and Mineral Research (2000), 15(6), 1024-1032

CODEN: JBMREJ; ISSN: 0884-0431

PUBLISHER: American Society for Bone and Mineral Research

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Effective bone remodeling requires the coordination of bone matrix deposition by osteoblastic cells, which may occur via soluble mediators or via direct intercellular communication. We have previously identified two mechanisms by which rat osteoblastic cell lines coordinate calcium signaling among cells: autocrine activation of P2 (purinergic) receptors leading to release of intracellular calcium stores, and gap junction-mediated communication resulting in influx of extracellular calcium. In the current work we asked whether human osteoblastic cells (HOB) were capable of mech. induced intercellular calcium signaling, and if so, by which mechanisms. Upon mech. stimulation, human osteoblasts propagated fast intercellular calcium waves, which required activation of P2 receptors and release of intracellular calcium stores but did not require calcium influx or gap junctional communication. After the fast intercellular calcium waves were blocked, we observed slower calcium waves that were dependent on gap junctional communication and influx of extracellular calcium. These results show that human osteoblastic cells can propagate calcium signals from cell to cell by two markedly different mechanisms and suggest that these two pathways may serve different purposes in coordinating osteoblast functions.

REFERENCE COUNT: 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L56 ANSWER 19 OF 20 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 1998:714439 CAPLUS Full-text

DOCUMENT NUMBER: 130:93180

TITLE: Multiple mechanisms for intercellular calcium waves

AUTHOR(S): Steinberg, Thomas H.; Civitelli, Roberto; Beyer, Eric C.; Jorgensen, Niklas R.; Cao, Dongrong; Geist, Steven T.; Lin, George

CORPORATE SOURCE: Washington University School of Medicine, St. Louis, MO, USA

SOURCE: Gap Junctions, Proceedings of the International Gap Junction Conference, 8th, Key Largo, Fla., July 12-17, 1997 (1998), Meeting Date 1997, 271-275. Editor(s): Werner, Rudolf. IOS Press: Amsterdam, Neth.

CODEN: 66XYAX

DOCUMENT TYPE: Conference

LANGUAGE: English

AB Many cells coordinate calcium signaling by propagating intercellular calcium waves. We have studied mech.-induced intercellular calcium waves in osteoblastic cells, insulinoma cells, and tracheal epithelial cells and have detected three distinct mechanisms for the propagation of these waves. The most widespread mechanism for the propagation of intercellular calcium waves in these cells is stimulation of P2U purinergic receptors by extracellular ATP, which appears to be secreted by the stimulated cells. Thus, in the UMR rat osteoblastic cell line, the RIN rat insulinoma cell line, and hamster tracheal epithelial cells, intercellular calcium waves do not require gap junctional communication and are inhibited by the P2U-blocker suramin or desensitization of P2U receptors by prior addition of ATP. We have also identified two gap junction-dependent mechanisms for intercellular calcium waves, neither of which require IP3-mediated release of intracellular calcium stores. In RIN cells transfected with connexin43, gap junction-mediated calcium waves are blocked by inhibiting L-type calcium channels or by preventing membrane depolarization and appear to be mediated by gap junctional elec. coupling. In contrast, ROS cells propagate gap junction-mediated calcium waves that require influx of calcium across the plasma membrane, but do not require membrane depolarization. Gap junction-mediated and ATP-mediated mechanisms may coordinate calcium waves in diverse settings.

REFERENCE COUNT: 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L56 ANSWER 20 OF 20 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 1997:689393 CAPLUS Full-text

DOCUMENT NUMBER: 128:2188

TITLE: ATP- and gap junction-dependent intercellular calcium signaling in osteoblastic cells

AUTHOR(S): Jorgensen, Niklas R.; Geist, Steven T.; Civitelli, Roberto; Steinberg, Thomas H.

CORPORATE SOURCE: Department of Internal Medicine, Washington University School of Medicine, St. Louis, MO, 63110, USA

SOURCE: Journal of Cell Biology (1997), 139(2), 497-506

CODEN: JCLBA3; ISSN: 0021-9525

PUBLISHER: Rockefeller University Press

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Many cells coordinate their activities by transmitting rises in intracellular calcium from cell to cell. In nonexcitable cells, there are currently two models for intercellular calcium wave propagation, both of which involve release of inositol triphosphate (IP3)-sensitive intracellular calcium stores. In one model, IP3 traverses gap junctions and initiates the release of intracellular calcium stores in neighboring cells. Alternatively, calcium waves may be mediated not by gap junctional communication, but rather by autocrine activity of secreted ATP on P2 purinergic receptors. We studied mech. induced calcium waves in two rat osteosarcoma cell lines that differ in the gap junction proteins they express, in their ability to pass microinjected dye from cell to cell, and in their expression of P2Y2 (P2U) purinergic receptors. ROS 17/2.8 cells, which express the gap junction protein connexin43 (Cx43), are well dye coupled, and lack P2U receptors, transmitted slow gap junction-dependent calcium waves that did not require release of intracellular calcium stores. UMR 106-01 cells predominantly express the gap junction protein connexin 45 (Cx45), are poorly dye coupled, and express P2U receptors; they propagated fast calcium waves that required release of intracellular calcium stores and activation of P2U purinergic receptors, but not gap junctional communication. ROS/P2U transfectants and UMR/Cx43 transfectants expressed both types of calcium waves. Gap junction-independent, ATP-dependent intercellular calcium waves were also seen in hamster tracheal epithelia cells. These studies demonstrate that activation

of P2U purinergic receptors can propagate intercellular calcium, and describe a novel Cx43-dependent mechanism for calcium wave propagation that does not require release of intracellular calcium stores by IP3. These studies suggest that gap junction communication mediated by either Cx43 or Cx45 does not allow passage of IP3 well enough to elicit release of intracellular calcium stores in neighboring cells.

REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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FILE 'CAPLUS' ENTERED AT 10:46:57 ON 26 SEP 2007

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FILE 'REGISTRY' ENTERED AT 10:47:16 ON 26 SEP 2007

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57381-26-7/BI OR 602-07-3/BI OR 7782-44-7/BI)

L3 13831 SEA ABB=ON PLU=ON ?HYDROXYACET?/CNS  
L4 0 SEA ABB=ON PLU=ON L2 AND L3  
L5 40 SEA ABB=ON PLU=ON L3 AND ?TYROSIN?/CNS  
L6 40 SEA ABB=ON PLU=ON L5 AND ?ACET?/CNS  
L7 40 SEA ABB=ON PLU=ON L6 AND ?HYDROX?/CNS  
L8 2 SEA ABB=ON PLU=ON L7 AND ?ASPARAGIN?/CNS  
D SCA  
L9 15 SEA ABB=ON PLU=ON L7 AND SQL>1  
L\*\*\* DEL 25277 S HIS

L10 8 SEA ABB=ON PLU=ON L9 AND SQL<15  
D SCA  
L11 8312 SEA ABB=ON PLU=ON "HYDROXYACETYL"  
L12 0 SEA ABB=ON PLU=ON L11 AND L2  
L13 20 SEA ABB=ON PLU=ON L2 AND NR=1  
L14 14 SEA ABB=ON PLU=ON L13 AND ?ASPARAGIN?/CNS AND ?TYROSIN?/CNS  
D SCA  
L15 1 SEA ABB=ON PLU=ON L14 AND C15H20N4O6/MF  
D SCA  
L16 1 SEA ABB=ON PLU=ON "ACETYLHYDROXYACETYL"  
D SCA  
L17 STR

FILE 'BEILSTEIN' ENTERED AT 12:54:08 ON 26 SEP 2007

L18 STR L17  
L19 1 SEA SSS SAM L18

FILE 'REGISTRY' ENTERED AT 13:01:20 ON 26 SEP 2007

L20 1 SEA SSS SAM L18  
L21 2 SEA SSS FUL L18  
D SCA  
D QUE  
L22 0 SEA ABB=ON PLU=ON L21 AND L14  
D QUE L21  
L23 STR L18  
L24 14 SEA SSS SAM L23  
L25 1260 SEA SSS FUL L23  
L26 STR L23  
L27 0 SEA SUB=L25 SSS SAM L26  
L28 2 SEA SUB=L25 SSS FUL L26  
D SCA  
L29 1 SEA ABB=ON PLU=ON L28 AND C17H22N4O7/MF  
D SCA  
L30 235 SEA ABB=ON PLU=ON C15H20N4O6/MF  
L31 1 SEA ABB=ON PLU=ON L30 AND L25  
D SCA  
D L29

FILE 'BEILSTEIN' ENTERED AT 13:11:03 ON 26 SEP 2007

L32 STR L23

FILE 'BEILSTEIN' ENTERED AT 13:12:02 ON 26 SEP 2007

L33 0 SEA SSS FUL L32

FILE 'MARPAT' ENTERED AT 13:12:16 ON 26 SEP 2007

L34 0 SEA SSS SAM L32  
L35 1 SEA SSS FUL L32  
L36 1 SEA ABB=ON PLU=ON L35/COM  
D SCA  
SEL PN

FILE 'CAPLUS' ENTERED AT 13:17:18 ON 26 SEP 2007

L37 1 SEA ABB=ON PLU=ON (WO2007007060/PN OR US2007123469/PN)  
L38 0 SEA ABB=ON PLU=ON L37 AND L1  
L39 1 SEA ABB=ON PLU=ON L29  
L40 1 SEA ABB=ON PLU=ON L37 AND L39

FILE 'MARPAT' ENTERED AT 13:18:52 ON 26 SEP 2007

FILE 'MARPAT' ENTERED AT 13:18:54 ON 26 SEP 2007



L41 STR L32  
 L42 0 SEA SSS SAM L41  
 L43 1 SEA SSS FUL L41  
 L44 1 SEA ABB=ON PLU=ON L43/COM

FILE 'BEILSTEIN' ENTERED AT 13:20:55 ON 26 SEP 2007

L45 0 SEA SSS FUL L41

FILE 'CAPLUS' ENTERED AT 13:21:26 ON 26 SEP 2007

D QUE L39  
 D L39 IBIB ABS HITSTR

FILE 'MARPAT' ENTERED AT 13:21:42 ON 26 SEP 2007

D QUE L44  
 D L44 IBIB ABS QHIT TOT

FILE 'CAPLUS' ENTERED AT 13:22:41 ON 26 SEP 2007

E LARSEN B/AU

L46 335 SEA ABB=ON PLU=ON ("LARSEN B"/AU OR "LARSEN B A"/AU OR  
 "LARSEN B B"/AU OR "LARSEN B DUE"/AU OR "LARSEN B H"/AU OR  
 "LARSEN B HVOLBAEK"/AU OR "LARSEN B K"/AU OR "LARSEN B L"/AU  
 OR "LARSEN B M"/AU OR "LARSEN B R"/AU OR "LARSEN B RICHTER"/AU  
 OR "LARSEN B RIIS"/AU OR "LARSEN B S"/AU OR "LARSEN B T"/AU OR  
 "LARSEN B V"/AU OR "LARSEN BJARNE"/AU OR "LARSEN BJARNE D"/AU  
 OR "LARSEN BJARNE DUE"/AU OR "LARSEN BJARNE E"/AU OR "LARSEN  
 BJARNE N"/AU OR "LARSEN BJARNE NYHOLM"/AU OR "LARSEN BJARNE  
 RUDOLF EBBESKOV"/AU)

E PETERSEN J/AU

L47 639 SEA ABB=ON PLU=ON ("PETERSEN J"/AU OR "PETERSEN J A"/AU OR  
 "PETERSEN J A K"/AU OR "PETERSEN J B"/AU OR "PETERSEN J B  
 B"/AU OR "PETERSEN J BRAMMER"/AU OR "PETERSEN J C"/AU OR  
 "PETERSEN J CLAINE"/AU OR "PETERSEN J D"/AU OR "PETERSEN J  
 F"/AU OR "PETERSEN J F W"/AU OR "PETERSEN J G L"/AU OR  
 "PETERSEN J G LITSKE"/AU OR "PETERSEN J H"/AU OR "PETERSEN J  
 J"/AU OR "PETERSEN J KAAS"/AU OR "PETERSEN J L"/AU OR "PETERSEN  
 J L W"/AU OR "PETERSEN J LYG"/AU OR "PETERSEN J M"/AU OR  
 "PETERSEN J N"/AU OR "PETERSEN J O"/AU OR "PETERSEN J OTZEN"/AU  
 OR "PETERSEN J R"/AU OR "PETERSEN J RAAGAARD"/AU OR "PETERSEN  
 J RGEN"/AU OR "PETERSEN J ROED"/AU OR "PETERSEN J S"/AU OR  
 "PETERSEN J STYHR"/AU OR "PETERSEN J U H"/AU OR "PETERSEN J  
 V"/AU OR "PETERSEN J W"/AU OR "PETERSEN J WESTPHAL"/AU OR  
 "PETERSEN J WULFF"/AU OR "PETERSEN JORGEN"/AU OR "PETERSEN  
 JORGEN B"/AU OR "PETERSEN JORGEN F"/AU OR "PETERSEN JORGEN  
 H"/AU OR "PETERSEN JORGEN HOLM"/AU OR "PETERSEN JORGEN  
 LORENZO"/AU OR "PETERSEN JORGEN S"/AU OR "PETERSEN JORGEN  
 SOBERG"/AU OR "PETERSEN JORGEN SOEBERG"/AU)

E MEIER E/AU

L48 119 SEA ABB=ON PLU=ON ("MEIER E"/AU OR "MEIER E A"/AU OR "MEIER  
 E F"/AU OR "MEIER E G"/AU OR "MEIER E J J"/AU OR "MEIER E M  
 M"/AU OR "MEIER E P"/AU OR "MEIER E V"/AU OR "MEIER EDDI"/AU  
 OR "MEIER EDDIE"/AU)

E KJOLBYE A/AU

L49 9 SEA ABB=ON PLU=ON ("KJOLBYE ANNE"/AU OR "KJOLBYE ANNE  
 LOUISE"/AU)

E JORGENSEN N/AU

L\*\*\* DEL 0 S E-11,E24-25

L50 79 SEA ABB=ON PLU=ON ("JORGENSEN N"/AU OR "JORGENSEN N A"/AU OR  
 "JORGENSEN N E"/AU OR "JORGENSEN N O"/AU OR "JORGENSEN N O  
 G"/AU OR "JORGENSEN N P"/AU OR "JORGENSEN N R"/AU OR "JORGENSEN  
 N RYE"/AU OR "JORGENSEN N V"/AU OR "JORGENSEN NIKLAS R"/AU OR

"JORGENSEN NIKLAS RYE"/AU)  
 E NIELSEN M/AU

L51 781 SEA ABB=ON PLU=ON ("NIELSEN M"/AU OR "NIELSEN M A"/AU OR  
 "NIELSEN M B"/AU OR "NIELSEN M BROENDSTED"/AU OR "NIELSEN M  
 C"/AU OR "NIELSEN M D"/AU OR "NIELSEN M DAMKJAER"/AU OR  
 "NIELSEN M E"/AU OR "NIELSEN M F"/AU OR "NIELSEN M FAMKJAER"/AU  
 OR "NIELSEN M FOLMER"/AU OR "NIELSEN M G"/AU OR "NIELSEN M  
 H"/AU OR "NIELSEN M HILMER"/AU OR "NIELSEN M JULIN"/AU OR  
 "NIELSEN M K"/AU OR "NIELSEN M KAY"/AU OR "NIELSEN M KIM"/AU  
 OR "NIELSEN M L"/AU OR "NIELSEN M LYKKEGAARD"/AU OR "NIELSEN M  
 LYKKEGARD"/AU OR "NIELSEN M M"/AU OR "NIELSEN M MEEDOM"/AU OR  
 "NIELSEN M N"/AU OR "NIELSEN M O"/AU OR "NIELSEN M P"/AU OR  
 "NIELSEN M S"/AU OR "NIELSEN M S WEBER"/AU OR "NIELSEN M T"/AU  
 OR "NIELSEN M THELLEFSEN"/AU OR "NIELSEN M V"/AU OR "NIELSEN  
 MORTEN"/AU OR "NIELSEN MORTEN A"/AU OR "NIELSEN MORTEN H"/AU  
 OR "NIELSEN MORTEN HJULER"/AU OR "NIELSEN MORTEN HOLTEGAARD"/AU  
 OR "NIELSEN MORTEN M"/AU OR "NIELSEN MORTEN MUHLIG"/AU OR  
 "NIELSEN MORTEN MUNCH"/AU OR "NIELSEN MORTEN S"/AU OR "NIELSEN  
 MORTEN SCHAK"/AU OR "NIELSEN MORTEN SCHALLBURG"/AU OR "NIELSEN  
 MORTEN STORGAARD"/AU OR "NIELSEN MORTEN T"/AU OR "NIELSEN  
 MORTEN THELLEFSEN"/AU OR "NIELSEN MORTON"/AU)  
 E HOLSTEIN-RATHLOU/AU  
 E HOLSTEIN RATHLOU/AU

L52 80 SEA ABB=ON PLU=ON ("HOLSTEIN RATHLOU N H"/AU OR "HOLSTEIN  
 RATHLOU N H N H"/AU OR "HOLSTEIN RATHLOU NIELS H"/AU OR  
 "HOLSTEIN RATHLOU NIELS HENRIK"/AU)  
 E MARTINS J/AU

L53 379 SEA ABB=ON PLU=ON ("MARTINS J"/AU OR "MARTINS J A"/AU OR  
 "MARTINS J A C"/AU OR "MARTINS J AVILA"/AU OR "MARTINS J B"/AU  
 OR "MARTINS J B L"/AU OR "MARTINS J BENUZZI"/AU OR "MARTINS J  
 C"/AU OR "MARTINS J C A"/AU OR "MARTINS J C F"/AU OR "MARTINS  
 J D"/AU OR "MARTINS J E C"/AU OR "MARTINS J F"/AU OR "MARTINS  
 J F P"/AU OR "MARTINS J G O"/AU OR "MARTINS J I"/AU OR  
 "MARTINS J I F PAIVA"/AU OR "MARTINS J INACIO"/AU OR "MARTINS  
 J K"/AU OR "MARTINS J L"/AU OR "MARTINS J L RODRIGUES"/AU OR  
 "MARTINS J L S"/AU OR "MARTINS J M"/AU OR "MARTINS J M F"/AU  
 OR "MARTINS J M S"/AU OR "MARTINS J M V"/AU OR "MARTINS J  
 MANUEL LEAO"/AU OR "MARTINS J MARTIN"/AU OR "MARTINS J O"/AU  
 OR "MARTINS J P"/AU OR "MARTINS J P S"/AU OR "MARTINS J R"/AU  
 OR "MARTINS J R M"/AU OR "MARTINS J S"/AU OR "MARTINS J S  
 S"/AU OR "MARTINS J S SA"/AU OR "MARTINS J V"/AU OR "MARTINS J  
 V C"/AU OR "MARTINS J VANDERLEI"/AU OR "MARTINS JAMES"/AU OR  
 "MARTINS JAMES B"/AU)

L54 2371 SEA ABB=ON PLU=ON (L46 OR L47 OR L48 OR L49 OR L50 OR L51 OR  
 L52 OR L53)

L55 29 SEA ABB=ON PLU=ON L54 AND ?INTERCELL?

L56 20 SEA ABB=ON PLU=ON L55 AND ?COMMUN?  
 D QUE L56  
 D L56 IBIB ABS TOT